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Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
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Ref: INTERNATIONAL CONFERENCE on HARMONIZATION; DRAFT GUIDANCE on Q9 QUALITY RISK MANAGEMENT RELEASED FOR CONSULTATION ON MARCH 22, 2005; PUBLISHED AUGUST 8, 2005 [Docket No. 2005D-0288]

Dear Sir/Madam:

PDA is pleased to provide comments to FDA on ICH Q9 Quality Risk Management released for consultation on March 22, 2005. PDA is a non-profit international professional association of more than 10,000 individual member scientists having an interest in the fields of pharmaceutical, biological and device manufacturing and quality. The draft guidance provides principles and examples of tools for quality risk management that can be applied to all aspects of pharmaceutical quality throughout the lifecycle of drug substances, drug products, and biological and biotechnological products. The draft guidance is intended to enable regulators and industry to make more effective and consistent risk-based decisions. PDA wishes to thank the Agency for the opportunity to provide comments on this document.

PDA is optimistic that the publication of this document will provide industry with valuable resources and direction for managing a Quality Risk Management process. Detailed comments are provided in the attached Table. Topics are identified by topic or section number of the Draft Guidance. The following is a list of some of the major conclusions reached by the PDA review team.

1. We believe that a training program that includes case studies in the application of this document would benefit the industry as well as regulators.
2. PDA is concerned that, as written, this Guideline could lead to the practice of regulatory authorities wanting to audit results of internal risk management processes and procedures. As it is well accepted that one of the main goals of such processes is to allow industry to optimally strive for continual improvement, PDA recommends that the introductory language be revised to indicate that regulators will not audit all results of the Quality Risk Management process so that industry can use this process to work toward continual improvement.

PDA views this Guideline as a foundation document along with ICH Q8 and ICH Q10 (to be developed). Therefore, we believe it is of critical importance to ensure there is a clear and shared understanding between the regulatory authorities and industry of the concepts outlined in the Guideline and their practical application. We believe that all parties will benefit from continued dialogue around clarification, interpretation, and implementation of these concepts and we look forward to continuing to contribute to this discussion.

Sincerely,

Robert B. Myers
President, PDA

2005D-0288

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Section	Line/ paragraph	Current wording	Suggested Change (Suggested rewording)	Comment/Rationale/Reason for change	Critical/ Major /minor/ Editorial
General				Training: The application of risk management over the life cycle of a product, while not new, does have new ramifications. We believe consideration should be given into developing a comprehensive training program reviewing the guidance document, applications and case studies. The implementation of ICH Q9 would benefit from expository discussions and case studies by both regulators and industry representatives, including persons involved with the development of the document from several of the ICH parties	Critical
Explanatory text beginning of EU document				It is important that the legal implications of publishing this document as an annex to the EC GMP Guide are well understood. If publishing it as an annex means that the it becomes a mandatory requirement, then a more applicable method of publication should be found, for example as a Quality Working Party (QWP) guideline, in order to avoid misunderstandings and raise expectations. In addition the implications for veterinary products need to be evaluated, if this document is issued as an annex to the EU GMP guide. See also next comment.	Critical

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Explanatory text beginning of EU document			We propose Q9 should be offered to VICH before it is implemented in Europe for Vet product developers and manufacturers.	There are vast differences in risk between human and veterinary products, and even between different Vet products. So, even if Vet. activities should be able to take advantage of Q9, we would not support the proposed adoption of Q9 for Vet products without a unit of work to assess whether it should fully apply.	Critical
1	3rd paragraph, 4th sentence	high quality	safety and effectiveness	The ultimate goal of "high quality" of the drug is safe and effective drug. For clarity to all readers, spell it out.	minor
1	4th paragraph	It is not intended to create any new expectations beyond the current regulatory requirements	Add in Introduction 4th paragraph, last sentence "It is not intended to create any new expectations beyond the current regulatory requirements, neither is it intended that regulatory authorities will audit all results of internal risk management processes.	It is important that not all information produced by a Risk Management process should be shared with outside stakeholders. This has been discussed a lot in the area of Corporate Governance. The regulators should be interested in the pharma company having an integrated risk management process, but not require to see or audit all the information produced. The process would never work if all produced information must be shared with the outside stakeholders. There is a risk that this guideline paper could result in regulatory authorities demanding to audit all results of the internal risk management process.	Critical
1	5th paragraph, 2nd line	formal risk management	a formal (comprehensive, structured, and disciplined) risk management process	The terms formal and informal risk management may not always be understood. Some explanation is required to assure clarity.	Major

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2	1st sentence	all aspects	different stages or phases	The term "all aspects" appears to be very definitive. However, this guideline has also indicated in section 6 (4th paragraph, 4th sentence) that the examples should not be considered a definitive and exhaustive list. In addition, future innovative products may require new tools that are not known at this moment. Therefore, the claim to "all aspects" may not be accurate and should be deleted with the suggested change..	Major
3	Section Principles of quality risk management	This section was rewritten as: "Two primary principles of quality risk management are: The evaluation of the risk to quality should ultimately link back to the protection of the patient The level of effort, formality and documentation of the quality risk management process should be commensurate with the level of risk and be based on scientific knowledge."	Correct to:"Two primary principles of quality risk management are: The evaluation of the risk to quality should ultimately link back to the protection of the patient and be based on scientific knowledge. The level of effort, formality and documentation of the quality risk management process should be commensurate with the level of risk."	The underlined section in the second bullet point doesn't make sense, level of effort is not based on scientific knowledge. The addition of this statement was in a previous round of EFPIA comments and was intended to be added to the first bullet point after "protection of the patient".	Editorial

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4	title of figure	quality risk management process	risk management process	The figure below the title has labels with Risk Management but not Quality Risk Management. The process described in the figure is common to all risk management processes, not only quality risk management.	Major
4.1	1st paragraph, line 4	... resources are invovlved..	... resources are committed ...	Shows stronger emphasis for the effort.	minor
4.1	2nd paragraph	...by interdisciplinary teams dedicated to....	We suggest to add: "...interdisciplinary teams dedicated to *that particular* task."	We think there is a possible confusion in the interpretation of the sentence "...interdisciplinary teams dedicated to the task." It could be interpreted as requiring industry to set up a permanent interdisciplinary team with the sole responsibility of performing risk management. We believe the intent of this sentence is to indicate that, for certain projects, a team can be put together with members of different disciplines (e.g. Manufacturing, Quality Assurance, etc) to perform risk assessment and risk management for a finite period of time, for a particular project.	minor

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4.2	1st bullet	… …define the problem and/or risk question, including pertinent assumptions identifying the potential for risk and assemble background information and data on the potential hazard, harm …..	Move the fundamental questions defined under 4.3 " 1. What might go wrong? 2. what is the likelihood (probability it will go wrong? 3. What are the con+D25sequences (severity)? "into section 4.2 as sub bullets after 2nd bullet.	There is confusion and overlap between sections 4.2 and 4.3. The questions needed to define the problem should be included in section 4.2 and not in 4.3	Major
4.3	1st sentence	Quality risk assessments begin with a well-defined problem description or risk question…….define the problem and/or risk question, including pertinent assumptions identifying the potential for risk and assemble background information and data on the potential hazard, harm …..	Propose to delete the 3rd sentence in section 4.3 "Quality risk assessments begin with a well-defined problem description or risk question" and move the fundamental questions to section 4.2.Change 1st sentence to 4.3 to "Risk Assessment takes place after the problem and/or risk question has been defined and consists of the identification of hazards……"	There is confusion and overlap between sections 4.2 and 4.3. Section 4.2 states "define the problem and/or risk question, including pertinent assumptions identifying the potential for risk and assemble background information and data on the potential hazard, harm ….. This is basically repeated in section 4.3 with "Quality risk assessments begin with a well-defined problem description or risk question" and the 3 fundamental questions.	Major
4.3	heading of section 4.3	Risk Assessment	Quality Risk Assessment	Add the word "Quality" for consistency with other headings .	Major
4.3	bullets 1,2 3	add bullet #4	How detectable is it?	makes this similar to the ISPE model for assessing risk	minor

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4.3	3 bullets and risk analysis definition	The 3 questions were rewritten as: 1.What might go wrong? 2.What is the likelihood (probability) it will go wrong? 3. What are the consequences (severity)? (previously version stated "What is your ability to detect them")	Correct to: "***Risk analysis*** is the estimation of the risk associated with the identified hazards. It is the process that focuses on the second and third questions, seeking the likelihood that risks identified in risk identification might occur and an ability to detect them. "What are the consequences if they occur."	The text in ***Risk analysis*** was not reworded to be in-line with the change to question #3 to "What are the consequences". It was rewritten as: "***Risk analysis*** is the estimation of the risk associated with the identified hazards. It is the process that focuses on the second and third questions, seeking the likelihood that risks identified in risk identification might occur and an ability to detect them."	Editorial
4.3	Risk evaluation 4th paragraph	Risk evaluation compares the identified and analyzed risk against given risk criteria.	Risk evaluation compares the identified and analyzed risk against given risk acceptance criteria.	it is not clear what is meant by risk criteria, It would be more appropriate to compare with the risk acceptance criteria, thereby giving the risk evaluation a defined end point.	Major
4.3	Risk evaluation, 2nd sentence	probability and severity of a risk	probability of occurrence and severity of harm	Using the definition of risk is a much better guidance to the reader.	minor
4.3 - Risk Assessment, 4.4 Risk control, 4.5 Risk communicatio n			Detectability should be addressed by including a definition.	We realize that there is no specific section relating to harm detectability, as it exists in other guidance documents (e.g.. ISO 14971). While the term is not defined within the document, there are several tangential requirements incorporating it. We question whether there will be requirement from regulators for a formal risk assessment to include the ability to detect harm.	minor

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4.4	1st paragraph, 2nd bullet	reduce, control or eliminate risks	reduce, contain, or eliminate risks	These are ways to control risk. Using the word "control" here is redundant.	minor
4.4	2nd paragraph, last sentence	"Hence, it might be appropriate to revisit the risk assessment to identify and evaluate any possible change in risk	Revise the last sentence in the ***Risk Reduction*** section by adding underlined text as noted: "Hence, it might be appropriate to revisit the risk assessment to identify and evaluate any possible change in risk until an acceptable risk tolerance is determined."	Clarification is needed to ensure assessments are not repeatedly made without an end point.	Major
4.4	3rd paragraph 1st sentence	Risk acceptance is a decision to accept risk.	...decision to accept risk based on evaluation of risk determination to the predefined risk criteria.	Bring risk acceptance back to a criteria previously set.	Major
4.6	Risk review 1st paragraph, 3rd sentence	and a mechanism to perform periodic review of events should be implemented.	and a mechanism to perform a periodic review of events or monitoring, if needed, on an on-going basis should be implemented.	Review rather implies that the activity is carried out periodically, whereas in some cases risk monitoring, being carried out continuously may be more appropriate.	Major
5.3	last sentence (under potential areas of use(s))	in the manufacturing process	not only in the manufacturing process but also in other life cycle phases	The 7 principles of HACCP could be applied in many processes other than just manufacturing. For example, product distribution process, product storage, supplier material control process, some HACCP principles could apply to product development too.	minor

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5.4	2nd paragraph (under potential areas of use(s))	Hazop can be applied to manufacturing processes....	Add the underlined text: "HAZOP can be applied to manufacturing processes, <u>including the outsourced production and formulation as well as the upstream suppliers,</u> equipment and facilities for drug substances and drug (medicinal) products."	When applying risk management to 'the manufacturing process' one must include the outsourced production and formulation as well as the upstream suppliers.	Major
7	General Comment: Definitions		In some cases (hazard, risk) there is reference to another standard, in other cases not. Wherever possible references should be given.	Clarity and Consistency	minor
7	Harm	Harm		It is noted that the definition of harm given is not consistent with the definition given in ISO/IEC Guide 51:1999 definition 3.1. Change definition for consistency to ISO/IEC definition unless this has this been done on purpose?	Critical
7	Definition of Quality System	Formalized system that documents the structure, responsibilities and procedures to achieve effective quality management	Suggest adding word "actions" as follows: Formalized system that documents the structure, responsibilities, procedures <u>and actions</u> to achieve effective quality management.	Clarity and accuracy	Major
7	Definition of Risk Assessment	Systematic process of organizing information,,,,,	Add at the end of the definition : "It consists of the identification of hazards and the analysis and evaluation of risks associated with exposure to those hazards."	Clarity . This definition is inconsistent with the text under 4.3. A reading of 4.3 would suggest from the first sentence that Risk Assessment is "The identification of hazards and the analysis and evaluation of risks associated with exposure to those hazards".	Major

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7	Definition of Risk Communicati on	Exchange of sharing of information	Delete "Exchange of..." at beginning of sentence	Clarity	minor
7	Definition of Risk Identification	Systematic use of information....	Delete "Systematic..." to read "Use of information to ..."	Clarity. Systematic is understood.	minor
7	Definition Risk Management	Systematic application of quality management policies	Delete definition for 'Risk Management'.	There are definitions for Risk Management and Quality Risk Management. It is suggested that both are not needed.	minor
7	Definition of Risk Review	Step in the risk management process	Suggest rewording: "Review of outputs/result of the risk management process to take into account new knowledge and experience."	Clarity: More consistent with text in 4.6.	minor
7	Definition of Trend	A statistical term referring to the direction.....	The definition of trend is not 'user friendly'. Propose to change it to : "The relatively constant movement of a variable throughout a period of time."	Clarity and utility	Major
7	Definition of Uncertainty	The inability to determine or the ambiguity in the true.....	Delete "..or the ambiguity in..." to read as: "The inability to determine the true state of a system..."	Clarity	minor

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Annex 1	Annex 1 1st sentence	This annex is intended to identify opportunities.....	Propose to replace the words "opportunities for the use of quality risk management principles" with "This Annex is intended to identify potential quality risk - contributing factors and risk control options where quality risk management principles by industry and regulators (e.g. for both inspections and submissions) can be used".	The word "opportunities" is not appropriate here. Opportunities are not created, rather risk management principles are used when necessary and when useful.	Major
Annex I, 1.1	1.1, Auditing/Inspection, 3rd bullet	Results of a company's quality risk management activities	Suggest changing bullet #3 from "Results of.." to "Robustness of a company's quality risk management activities"	External auditors will not have the results of risk management activities, but they may have some indication of how well a company integrates RM processes into their quality system.	Major
Annex I, 1.2	I.2. Assessment activities 3rd paragraph	...(e.g., parametric release, Process Analytical Technology (PAT))."	Suggest deletion of the statement "...(e.g., parametric release, Process Analytical Technology (PAT))."	As written, parametric release and PAT are represented as risks; rather then well known and existing tools and regulatory policies.	Major
Annex 1, I.6	I.6. Validation 1st paragraph	....using worst case approach	Suggest deletion of the statement at end of sentence "...using worst case approach."	As rewritten, the statement is perfectly clear and leaves room for inclusion of worst case where appropriate, and for the continued evolution of validation guidance underway by regulators.	Major
Annex 1, 1 6	Validation 3rd paragraph	To distinguish between critical process steps	Move 3rd paragraph to section Annex 1.3 Quality Risk Management as part of development.	This is part of I.3 Development	Editorial

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Annex 1, 1.9	1st sentence	To identify, assess and (re)evaluate....	Add a sentence to section 1.9 "Continuous Improvement" : "To identify and assess throughout the product lifecycle any areas of product quality and process robustness and efficiency which can lead to improvements."	Continuous improvement is an integrated part of Quality management. Add a sentence on Continuous Improvement to section1.1 in Annex 1. Also continuous improvement is not only about the critical parameters, it includes any aspect of the product and process quality and robustness.	Major
Annex 1, 1.9	1st sentence	To identify, assess and (re)evaluate....	change to "To identify, assess and (re-)evaluate any aspects of the product and process quality and robustness throughout the product lifecycle (e.g., as the product and process move from research, to development and throughout manufacturing.	Continuous improvement is not only about the critical parameters, it includes any aspect of the product and process quality and robustness.	Major
Annex1, 1.9	Diagram	Diagram	Delete the diagram	Delete the diagram, It does not add any information. The principle of continuous improvement will most probably be addressed completely in Q10 and it would be unfortunate to end up with different diagrams in different documents. Also it implies that supplements and variations are required for change control and periodic reviews. Technology transfer should also include knowledge transfer	Critical